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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,497	11/13/2001	Simeon M. Wrenn Jr.	12636-876	8627

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EXAMINER

LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 04/20/2004

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/763,497

Applicant(s)

WRENN JR., SIMEON M.

Examiner

Patrick T. Lewis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 August 2003.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-24,26,27,29 and 44-60 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 11-24,26,27,29 and 44-60 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II in a telephone conversation dated March 21, 2003 is acknowledged.

Applicant's Response dated August 8, 2003

2. In the Response filed August 8, 2003, claims 1-10, 25, 28, and 30-43 were canceled; claims 11, 13, 15-17, and 50 were amended; and claims 59-60 were added.

3. Claims 11-24, 26-27, 29, and 44-60 are pending. An action on the merits of claims 11-24, 26-27, 29, and 44-60 is contained herein below.

4. The objection to the specification has been withdrawn in view of applicant's response dated August 8, 2003.

5. The rejections of claims 11-24, 26-27, 29, and 44-58 under 35 U.S.C. 112, first paragraph, have been withdrawn.

6. The rejection of claims 11, 13-24, 26-27, 29, 44-52, and 54-59 under 35 U.S.C. 112, second paragraph, as it relates to the term "2'-deoxyadenosine analog" is maintained for the reason of record set forth in the Office Action dated April 8, 2003.

7. The rejection of claims 11, 16, 20, 46-47, 50-52, and 56-57 under 35 U.S.C. 102(b) as being anticipated by Bristol-Myers Squibb Company EP 0 524 579 A1 (BMS) has been withdrawn.

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8. The rejection of claims 11, 14, 16-17, 20, 24, 46, 49-50, 52, and 56 under 35 U.S.C. 102(b) as being anticipated by Schinazi et al. US 5,118,672 and Schinazi et al. US 5,159,067 has been withdrawn.

9. The rejection of claims 11-24, 26-27, 29, 46-47, 49-53, and 56-57 under 35 U.S.C. 103(a) as being obvious over BMS EP 0 524 579 in view of Carson et al. US 5,310,732 (Carson) and Gallagher US 5,366,960 (Gallagher) is maintained for the reasons of record as set forth in the Office Action dated April 8, 2003.

10. The rejection of claims 11, 16, 20, 44-48, 50-52, and 54-58 under 35 U.S.C § 103(a) as being obvious BMS EP 0 524 579 in view of The Merck Index, Twelfth Edition, **1996**, 2337 (Merck) has been withdrawn.

11. The rejection of claims 11, 13-20, 24, 26-27, 29, 46-47, 49-50, 52, and 56-57 under 35 U.S.C. 103(a) as being obvious over Schinazi et al. US 5,118,672 and Schinazi et al. US 5,159,067 in view of Itoh US 5,194,464 (Itoh) has been withdrawn.

12. The rejection of claims 11, 13-20, 24, 26-27, 29, 46-47, 49-50, 52, and 56-57 under 35 U.S.C. 103(a) as being obvious over Schinazi et al. US 5,118,672 and Schinazi et al. US 5,159,067 in view of Shimuzu et al. US 5,824,339 (Shimuzu) has been withdrawn.

13. The rejection of claims 11, 13-20, 24, 26-27, 29, 46-47, 49-50, 52, and 56-57 under 35 U.S.C. 103(a) as being obvious over Schinazi et al. US 5,118,672 and Schinazi et al. US 5,159,067 in view of Fuisz US 5,518,730 (Fuisz) has been withdrawn.

Objections/Rejections of Record Set Forth in Office Action dated April 8, 2003

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claims 11, 13-24, 26-27, 29, 44-52, and 54-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "2'-deoxyadenosine analog" renders claims in which it appears indefinite.

Applicant's arguments filed August 8, 2003 have been fully considered but they are not persuasive. Applicant argues that said term is well known in the art; however, in the absence of the specific modifications to the 2'-deoxyadenosine or distinct language to describe the analog, the term is indefinite, as it has not been particularly pointed out or distinctly articulated in the claims.

16. Claims 11-24, 26-27, 29, 46-47, 49-53, and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over BMS EP 0 524 579 in view of Carson et al. US 5,310,732 (Carson) and Gallagher US 5,366,960 (Gallagher).

Applicant's arguments filed August 8, 2003 have been fully considered but they are not persuasive. Applicant argues BMS fails to teach the treatment of the specific diseases recited in the claims, Carson does not teach orally administering a 2'-deoxyadenosine analog in combination with an agent that reduces acid concentration, and Gallagher fails to motivate one of ordinary skill in the art to modify BMS and Carson to arrive at the claimed invention.

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In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

BMS teaches the improvement of the acid stability of deoxypurine nucleosides involving enteric-coated formulations, inclusion of a buffer in the dosage form, and neutralization of the gastrointestinal tract by pretreatment with commercial antacids. It would have been obvious to one of ordinary skill in the art at the time of the invention to employ an agent that reduces the acid concentration in the stomach in combination with cladribine or pentostatin for the treatment of leukemia and diseases mediated by adenosine deaminase, respectively, as BMS teaches it would improve the acid stability of the active agent.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 11-24, 26-27, 29, 44-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,174,873. Although the conflicting claims are not identical, they are not patentably distinct from each other because they only differ in the scope to diseases treated (overlap). Particular pharmaceutical formulations are seen as a choice of experimental design and are well within the purview of one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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21. Claims 11-24, 26-27, 29, and 44-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over BMS EP 0 524 579 in view of Carson et al. US 5,310,732 (Carson); Gallagher US 5,366,960 (Gallagher); and The Merck Index, Twelfth Edition, **1996**, 2337 (Merck) in combination.

Applicant claims methods to treat a patient using acid labile 2'-deoxyadenosine analogs, and in particular pentostatin or cladribine, and an agent that reduces the acidic environment of the stomach, and in particular an antacid such as calcium carbonate, a H₂ inhibitor such as cimetidine, or proton pump inhibitor.

BMS teaches that the acid lability of 2',3'-dideoxypurine nucleosides and their triphosphates are well known in the art (page 2, lines 9-25). Approaches to improve the acid stability of these acid-labile antiviral nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with commercial antacids. Further, BMS teaches on page 3, lines 30-36, that the buffers applied as antacid agents include mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate, preferably with calcium carbonate using microcrystalline cellulose and polyplasdone XL10 for use as antiviral agents.

BMS does not specifically teach that analogs, pentostatin or cladribine, can be administered with the antacid. Further, BMS does not explicitly state that the compositions can be used in the treatment of hematological malignancies, solid tumors sensitive to 2'-deoxyadenosine analogs or adenosine deaminase inhibitors and

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autoimmune disease mediated by adenosine or adenosine deaminase, and in particular leukemia. Finally, BMS does not specifically disclose the particular pharmaceutical formulations.

Carson teaches 2'-halo-2-deoxyadenosine compounds, and in particular 2'-chloro-2'-deoxyadenosine, also known as cladribine, for the treatment of monocyte-mediated disorders, such as rheumatoid arthritis and multiple sclerosis. See abstract and column 6, lines 37-65. Further, in column 4, line 56 to column 5, line 14, Carson discloses that 2'-chloro-2'-deoxyadenosine has been found to be effective for the treatment of chronic lymphocytic leukemia and some T cell malignancies. Carson teaches in column 14, lines 53-59, that oral administration of the compound is a particularly attractive mode of administration; however, the bioactive compounds potentially decompose in the acidic conditions of the stomach. Carson teaches that this decomposition is due to the hydrolysis of the glycosidic bond under acidic conditions. In column 13, line 48 to column 14, line 41, Carson teaches various pharmaceutical formulations. In particular, in column 13, line 60 to column 14, line 3, Carson teaches liposomal formulations using phosphatidyl cholines. In column 14, lines 27-41, Carson teaches enteric formulations that serve to resist disintegration in the stomach and permits the active ingredient to pass intact into the duodenum. Examples of such enteric layers or coatings include cellulose acetate phthalate and the like.

Gallagher teaches pentostatin for the treatment of cerebral and cardiovascular disorders. See Abstract. Further, Gallagher teaches in column 2, lines 30-53 that pentostatin is a potent inhibitor of the enzyme adenosine deaminase. In column 7, line

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12 to column 8, line 2, Gallagher teaches various pharmaceutical formulations. In particular, in column 7, lines 30-34, Gallagher teaches that pentostatin can be administered with magnesium carbonate, methylcellulose, sodium carboxymethylcellulose and the like.

Merck teaches that cimetidine is a histamine H₂-receptor antagonist that inhibits gastric acid secretion.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use 2'-deoxyadenosine analogs with any compound known to neutralize acids of the gastrointestinal tract, as BMS teaches such attempts to increase the bioavailability of acid-labile nucleosides. A skilled artisan would have been motivated to do so in order to reduce the dosage of the active agent and related side effects. The skilled artisan would have had a reasonable expectation of success to make and use compositions with acid-labile 2'-deoxyadenosine analogs for their intended therapeutic use in combination with an agent known to neutralize the gastrointestinal tract. Particular pharmaceutical formulations, for example controlled release formulations, complexes with ion exchange resins and microspheres, are seen as a choice of experimental design, are well known to the skilled artisan and are within the purview of the prior art.

Conclusion

22. Claims 11-24, 26-27, 29, and 44-60 are pending. Claims 11-24, 26-27, 29, and 44-60 are rejected. No claims are allowed.

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23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

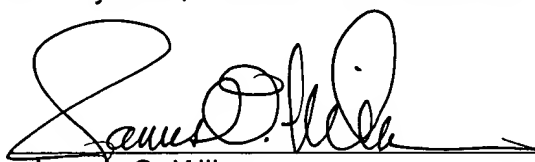
Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 10:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

ptl
April 16, 2004